Therefore, Rader, et al. does not anticipate the present invention. Applicants respectfully request the Examiner withdraw this rejection and duly allow all the claims.

2) Claims 19, 20, 23, and 28-35 are rejected under 35 U.S.C. § 102(b) as being anticipated by Sigma Chemie, product catalog (1996, Sigma Chemical Co., p. 271).

The Examiner alleges Sigma Chemical Co. teaches a method for treatment of atherosclerosis in a mammal comprising administering to said animal a safe and effective amount of a pharmaceutically acceptable carrier and an exogenously produced lysosomal acid lipase which targets a receptor site for uptake into lysosomes.

Applicants are confused by the Examiner's interpretation of this reference. The reference, provided by the Examiner, does not teach such a method. In fact, the cited reference does not teach any method of treatment of any disease or even lysosomal acid lipase. Applicants contend that the cited reference teaches, at best, a composition containing cholesterol esterase. As the Examiner is aware, cholesterol esterase is a different molecule from LAL. Applicants respectfully request the Examiner reevaluate the cited reference.

Once again, in order for a reference to anticipate a claimed invention, the reference must teach each and every limitation of the claimed invention. Applicants contend that Sigma Chemical Co. catalog (1996), page 271, does not anticipate the present invention. Therefore, Applicants respectfully request the Examiner withdraw this rejection and duly allow all the claims.

Rejection under 35 U.S.C. § 103

Claims 1-68 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rader, et al., in view of Du, et al. (AM J. Human Genet., vol. 57, 1995, page A178).

The Examiner alleges that Rader, et al. teach the aforementioned method, but does not teach administering a lipid hydrolyzing protein or polypeptide to reduce atherosclerosis plaques in mammals. The Examiner further alleges that Du, et al. teach a process to reduce atherosclerosis plaques in mammals and that it would be *prima facie* obvious for a person of ordinary skill in the art at the time the invention was made to modify the teachings of Rader, et al. by the additions of the teachings of Du, et al.

Applicants agree with the Examiner that Rader, et al. do not teach administering a lipid hydrolyzing protein or polypeptide to reduce atherosclerosis plaques in mammals. However, Applicants do not agree with the Examiner with regard to Du, et al. Applicants contend that Du, et al. teach several things. First, they teach that Wolman and cholesteryl ester storage (CESD) diseases are the result of point mutations, insertions, and deletions in the hLAL gene. Second, that CESD is associated with premature atherosclerosis. Third, and foremost, that there are at least four polymorphic forms of hLAL in normal human liver cDNA. All four polymorphic forms resulted in functional enzymes.

The present invention relates to a method for treating atherosclerosis and/or atherosclerotic plaques in a mammal comprising the administration to a mammal or into cells of a mammal, biologically active lipid hydrolyzing protein or polypeptide or a vector containing

and expressing a DNA sequence encoding a biologically active lipid hydrolyzing protein or polypeptide, the cells harboring the vector expressing the DNA sequence to produce the lipid hydrolyzing protein or polypeptide, and the cells secreting the lipid hydrolyzing protein or polypeptide which is taken up by other cells deficient in the lipid hydrolyzing protein or polypeptide.

To establish a *prima facie* case of obviousness, there must first be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify Rader, et al. or to combine Rader, et al. and Du, et al. Neither Rader. et al. nor Du, et al. teach or suggest a method for treating atherosclerosis or atherosclerotic plaque in mammals and it is unreasonable to believe that one of ordinary skill in the art would be motivated at the time the present invention was made to combine these two references to conceive and develop such a method.

Second, there must be a reasonable expectation of success in treating atherosclerosis by administering a biologically active lipid hydrolyzing protein or polypeptide to a mammal or a vector containing and expressing a DNA sequence encoding a biologically active lipid hydrolyzing protein or polypeptide into cells deficient in biologically active lipid hydrolyzing protein or polypeptide, the cells expressing the DNA sequence to produce the lipid hydrolyzing protein or polypeptide, and then secreting the lipid hydrolyzing protein or polypeptide, which is taken up by other cells deficient in the lipid hydrolyzing protein or polypeptide. No such expectation can be gleaned from Rader, et al. or Du, et al., individually or in combination.

Third, Rader, et al. and Du, et al. must teach or suggest all the claim limitations. Neither Rader, et al. nor Du, et al. teach or suggest a treatment for atherosclerosis and/or atherosclerotic plaque in mammals.

As the Examiner is aware, all three of the above mentioned criteria must be met in order to establish a *prima facie* case of obviousness. Neither of the cited references expressly or implicitly teach or suggest, individually or in combination, the present claimed invention or provide any motivation for one of ordinary skill in the art to modify the references or to combine the reference's teachings. Further, neither of the cited references provide any expectation of success of the present claimed invention. Lastly, neither of the cited references expressly or implicitly teach or suggest all the claim limitations of the present claimed invention.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness in the present claimed invention. Therefore, Applicants respectfully request the rejection be withdrawn and all the claims be duly allowed.

Conclusion

Applicants have amended their claims to more clearly define the invention and not to avoid cited art. Applicants have further provided descriptions of the cited art and distinguished the present claimed invention from the teachings of the cited references. None of the cited art anticipate or render the present invention *prima facie* obvious. WHEREFORE, reconsideration of this application, in view of the foregoing amendment and remarks, Applicants respectfully

request the rejections be withdrawn and all the instant claims 1-51, 53-55, and 58-68, be duly allowed.

Respectfully submitted,
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Claim 51 has been amended as follows:

51. (Amended) A method for providing biologically active lipid hydrolyzing protein or polypeptide, or mixtures thereof, to cells of a mammal having deficiency in said biologically active lipid hydrolyzing protein or polypeptide, said method comprising administration into said cells a vector [comprising] containing and expressing a DNA sequence encoding said biologically active lipid hydrolyzing protein or polypeptide, and expressing [the] said DNA sequence in said cells to produce said biologically active lipid hydrolyzing protein or polypeptide, wherein said cells harboring said vector secrete said biologically active lipid hydrolyzing protein or polypeptide which is taken up by other cells deficient in said lipid hydrolyzing protein or polypeptide.

Claim 58 has been amended as follows:

58. (Amended) The method of claim [56] 51 wherein the vector is a viral vector.

Claim 60 has been amended as follows:

60. (Amended) The method of claim [56] 51 wherein the vector is a plasmid.

Claim 61 has been amended as follows:

61. (Amended) The method of claim [56] 51 wherein the vector is a lipid vesicle.